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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,176	02/19/2002	Rainer K. Brachmann	004255.00008	9526

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,176	BRACHMANN, RAINER K.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *22-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☒ Claim(s) *1-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, further electing SEQ ID NO: 55, SEQ ID NO: 58 and SEQ ID NO: 51 in the reply filed on 8/13/04 is acknowledged. Claims 1-21 are under prosecution. Claims 22-51 are withdrawn from consideration as being drawn to a non-elected invention.

2. Claims 1-21 are objected to for specifically reciting non-elected inventions, namely non-elected sequences.

Priority

3. The amendment to the specification filed 11/13/03 has been entered noting a claim to the provisional application.

Information Disclosure Statement

4. The information disclosure statement filed 7/24/03 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the copies of the NCBI records provided are not complete copies as the right side of the pages are all cut off. The entire records are not represented. Therefore, these references could not be considered and were lined through on the 1449. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Allowable Subject Matter

5. Claim 21 is free of the prior art. The prior art does not teach or suggest an isolated nucleic acid which has the nucleic acid sequence shown in SEQ ID NO: 1. If claim 21 were amended to be in independent form and to overcome all of the 112 1st paragraph rejections set forth herein, the claim would be allowable.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn a "non-naturally occurring" nucleic acid molecule which encode wild-type human p53 protein as shown in SEQ ID NO: 55, wherein the nucleic acid employs a plurality of alternative codons to those present in naturally occurring wild-type human p53 coding sequence as shown in SEQ ID NO: 58, wherein at least a portion of said alternative codons provide additional unique restriction sites to the human p53 coding sequence.

The claims are problematic with regard to written description over the requirement that the nucleic acid molecule be "non-naturally occurring" insofar as this requirement may be construed so as to require that the particular coding sequence is not

sequence naturally occurring in any human cell. The specification teaches that a "naturally occurring" wild-type human p53 coding sequence may be any wild-type human p53 that is "naturally" found in humans and is characterized by wild-type p53 activity. However, the specification does not provide any written description guidance as to what physical characteristics differentiate the naturally occurring versus the non-naturally occurring molecules. That is, there is no written description that provides characteristics that differentiate these two classes of nucleic acid molecules. For example, the specification does not provide a structure/function relationship that can be applied to identifying naturally versus non-naturally occurring molecules that encode instant SEQ ID NO: 58. There are hundreds of thousands of possible nucleic acids that encode instant SEQ ID NO: 58, and the specification has not provided any guidance as to how to identify which of these are "naturally occurring" versus those that are not. This distinction is key to discerning the scope of the instant claimed invention. If one is attempting to make molecules that are within the scope of the claimed invention and is in a laboratory creating molecules that encode SEQ ID NO: 58, have added restriction sites, and are not SEQ ID NO: 55 (meeting all of the structural limitations of the instant claims) it is not possible to know, based on the teachings of the specification, if this molecule would be a "naturally occurring" molecule that would be found in some human cell somewhere. The disclosure of the specification does not set forth sufficient guidance to adequately describe the claimed set of nucleic acid molecules. Therefore, the claims are rejected for lacking written description.

Applicant is cautioned that the removal of the requirement "non-naturally occurring" from instant claim 1 (without further amendment) will likely lead to the setting forth of a different written description rejection.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farrell *et al.* (The EMBO Journal, Vol. 10, No. 10, p. 2879-2887, 1991) as supported by GenBank Accession (X60012, 23 June 1994), and further in view of Seed *et al.* (US 6114148).

Farrell *et al.* teach an isolated nucleic acid encoding instant SEQ ID NO: 55. The molecule taught by Farrell *et al.* is non-naturally occurring because it has been isolated and placed in an expression vector, and both of these processes result in nucleic acid molecules that are not in their naturally occurring form. Farrell *et al.* teach that the nucleic acid sequences that they isolated are disclosed within the GenBank database, with record X60012 being one of the molecules that they disclose (see Farrell *et al.*, p. 2885, Table 2 description). Farrell *et al.* exemplify the expression of this molecule in mammalian cells (p. 2883).

Farrell *et al.* do not teach a nucleic acid molecule that employs a plurality of alternative codons to those present in instant SEQ ID NO: 58, as the coding sequence

taught by Farrell *et al.* is identical to the coding sequence taught in instant SEQ ID NO: 58.

Seed *et al.* teach nucleic acid molecules encoding human proteins in which the natural gene encoding the protein has been replaced by a preferred codon encoding the same amino acid for expression of the protein in prokaryotic cells and mammalian cells (Col. 1-2). Seed *et al.* teach that under some circumstances, such as to permit the introduction of a restriction site, it may be desirable to replace non-preferred codons with less preferred codons (Col. 2), and Seed *et al.* teach methods in which at least 90% of the non-preferred codons are replaced (Col. 2). Seed *et al.* teach an advantage of producing the modified coding sequences is that the replacement of codons should yield genes capable of higher level expression in mammalian cell culture (Col. 3). Seed *et al.* exemplify modified coding sequences which contain unique restriction sites at approximately 100 base pair intervals (Col. 7, lines 60-65), and further teach that the addition of restriction sites can simplify manipulation of the resulting gene (Col. 11, lines 29-31) or to facilitate insertion of the resultant sequence into appropriate vectors (Col. 24, lines 25-30).

With regard to claims 3 and 4, these require that "at least a portion" of said alternate codons are more preferred for usage in yeast or bacterial cells. Seed *et al.* teach for example, the use of the codon GTG for valine, a codon which is also preferred in both yeast cells (*S. frugiperda*) and bacterial cells (*E. coli*).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the nucleic acid taught by Farrell *et al.* so as to have used alternative codons as provided by Seed *et al.* in order to provide a molecule with increased

expression in mammalian cells for further study of the encoded p53 molecule, for example to study function of the encoded protein in in vitro or in vivo assays. One would have been motivated to modify the molecule taught by Seed *et al.* to engineer the molecule encoding SEQ ID NO: 55 so as to have included additional restriction sites throughout the molecule, as directed by Seed *et al.* in order to provide a molecule that is able to be easily manipulated for future study. With regard to claims 5-14 which require different numbers of alternative codons to be used, the sequence taught by Farrell *et al.* contains at least 193 codons that are not those "preferred" according to Seed *et al.* It would have been obvious to have modified any or all of these codons using the guidance provided by Seed *et al.* Likewise, it would have been obvious to have included multiple restriction sites (referring to claims 15-20) following the guidance of Seed *et al.* in order to have provided additional means within the sequence for manipulation of the sequence and for assembly of the synthetically produced fragments. The manipulation of the sequence taught by Farrell *et al.* using the guidance taught by Seed *et al.* would necessarily have resulted in the replacement of codons in the sequence taught by Farrell *et al.* with at least a portion of alternative codons that are preferred for usage in mammalian, yeast and bacterial cells. Therefore, in view of the teachings of Farrell *et al.* in view of Seed *et al.*, the rejected claims are prima facie obvious.

10. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farrell *et al.* (The EMBO Journal, Vol. 10, No. 10, p. 2879-2887, 1991) as supported by GenBank Accession (X60012, 23 June 1994), and further in view of Weiss (US 6277322).

Farrell *et al.* teach an isolated nucleic acid encoding instant SEQ ID NO: 55. The molecule taught by Farrell *et al.* is non-naturally occurring because it has been isolated and placed in an expression vector, and both of these processes result in nucleic acid molecules that are not in their naturally occurring form. Farrell *et al.* teach that the nucleic acid sequences that they isolated are disclosed within the GenBank database, with record X60012 being one of the molecules that they disclose (see Farrell *et al.*, p. 2885, Table 2 description). Farrell *et al.* exemplify the expression of this molecule in mammalian cells (p. 2883).

Farrell *et al.* do not teach a nucleic acid molecule that employs a plurality of alternative codons to those present in instant SEQ ID NO: 58, as the coding sequence taught by Farrell *et al.* is identical to the coding sequence taught in instant SEQ ID NO: 58.

Weiss teaches the modification of genes encoding lysyl oxidase for expression in non-mammalian host cells specifically to optimize codon usage in such cells as E. coli and S. cerevisiae (Col. 3). Weiss further teaches that even when expressin human genes in human or mammalian cell lines modification of codons can still be beneficial to produce enhanced levels of the protein of interest (Col. 7-8). Weiss gives guidance throughout as to how to modify the coding sequence to increase output of this molecule to obtain the benefits of high production of the encoded polypeptide in host cells. Weiss teaches that the synthetic polynucleotides are generated by mutating the native nucleotide sequence so that all or some codons which hamper expression in the expression system are replaced with more favorable codons (Col. 7). Further, Weiss teaches the benefits of including restriction sites into the polynucleotide, including to facility assembly of the

polynucleotide, for subcloning, to provide sites for later introduction of modifications, and to facilitate confirmation of correct assembly (Col. 9).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the nucleic acid taught by Farrell *et al.* so as to have used alternative codons as provided by Weiss in order to provide a molecule with increased expression in mammalian cells for further study of the encoded p53 molecule, for example to study function of the encoded protein in in vitro or in vivo assays. One would have been motivated to modify the molecule taught by Weiss to engineer the molecule encoding SEQ ID NO: 55 so as to have included additional restriction sites throughout the molecule, as directed by Weiss in order to provide a molecule that is able to be easily manipulated for future study. With regard to claims 5-14 which require different numbers of alternative codons to be used, it would have been prima facie obvious to have modified all of the potential "non-preferred" codons for a given organism in order to obtain high expression in an alternate host system using the guidance provided by Weiss. Likewise, it would have been obvious to have included multiple restriction sites (referring to claims 15-20) following the guidance of Weiss in order to have provided additional means within the sequence for manipulation of the sequence and for assembly of the synthetically produced fragments. The manipulation of the sequence taught by Farrell *et al.* using the guidance taught by Weiss would necessarily have resulted in the replacement of codons in the sequence taught by Farrell *et al.* with at least a portion of alternative codons that are preferred for usage in mammalian, yeast and bacterial cells. Therefore, in view of the teachings of Farrell *et al.* in view of Weiss , the rejected claims are prima facie obvious.

Conclusion

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

12. Enclosed is a print out of the website "Preferred Codons for Selected Species" which gives preferred codons for a number of different species, including the bacteria *E. coli* and the yeast *S. frugiperda*.

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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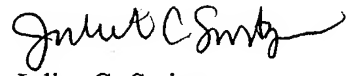

Juliet C. Switzer
Examiner
Art Unit 1634

October 15, 2004